REMARKS

Claims 34-37 and 53-59 are pending and claims 35-37, 55-57 and 59 are withdrawn.

Claim Rejections – 35 USC § 102(e)

Claim 34 is rejected under 35 USC 102(e) as being anticipated by US Patent No. 6,335,155 (Wells).

Applicants urge that their priority claim to US Application No. 09/049,754, now US Patent No. 6,344,330 ('US '330), precludes the use of Wells as a prior art reference. The earliest priority date of the present application, which is that of US Application No. 09/049,754, is March 27, 1998, whereas the filing date of Wells is June 26, 1998.

The Examiner states that Wells discloses the following:

(1) "combining said biological target molecule with one or more members of a library of small, non-oligomeric soluble, synthetic organic ligand candidates";

(2) "Other embodiments of the above described methods employ libraries of organic compounds which comprise . . . disulfides";

(3) "Libraries of organic compounds which find use herein will generally comprise at least 2 organic compounds, often at least about 25 different organic compounds, . . . preferably at least about 5000 or more different organic compounds"; and

(4) "combining [i.e. mixing] said biological target molecule with one or more members of a library".

Analogous to this disclosure, US '330 discloses the following:

(1) A library of small organic ligand candidates that are soluble in aqueous solution. (See, inter alia, column 5, lines 28-32 and column 6, lines 34-39.);

(2) Library compounds can include disulfides. (See, inter alia, column 6, lines 17-34);

(3) "Populations of organic compounds [i.e. a library] which find use herein will will generally comprise at least 2 organic compounds, often at least about 25 different organic compounds, . . . more preferably at least about 5000 different organic compounds." (See, inter alia, column 6, line 66 to column 7, line 6); and

(4) "Populations may be selected or constructed such that . . . two or more members of the population may be combined if methods for deconvolution are readily available." (See, inter alia, column 7, lines 8 -14.)

Therefore, the disclosure of US Application No. 09/049,754 is sufficient to prevent Wells from anticipating claim 34.

Claim Rejections – 35 USC § 103(a)

Claims 34, 53 and 54 are rejected under 35 USC 103(a) as being obvious over US Patent No. 6,552,060 (Kirkpatrick) and Konings, *J. Med. Chem.* 1996, 39, 2710-2719. Applicants urge that the claims are patentable over this combination of references for the following reasons.

To establish a *prima facie* case of obviousness, there must be (1) motivation to combine or modify references, (2) a reasonable expectation of success and (3) a teaching or suggestion of all the elements of the claims. As described more fully below, the combination of Kirkpatrick and Konings provides none of these required elements.

Kirkpatrick and Konings would not have motivated one to arrive at the present invention due to complications of the measuring assays and the potential for disulfide exchange of the active agents

The Kirkpatrick patent relates to compounds that modulates a cell's redox state. A key factor in the redox state of a cell is the oxidative state of select cysteine residues on certain proteins, which is difficult to detect directly because the post-translational modification of cysteines is readily reversed when the cell contents are exposed to extra-cellular oxidizing conditions. (Kirkpatrick, column 1, lines 29-34).

Specifically, Kirkpatrick discloses asymmetric disulfide compounds of the general formula R_1-S-S-R_2. These compounds affect the thioredoxin redox couple, comprising primarily of thioredoxin and thioredoxin reductase, which in turn affect the redox state of cells. The redox state of thioredoxin appears to be a key regulatory event affecting signaling in both the cellular proliferation and apoptosis pathways. Because thioredoxin either acts as a growth factor or enhances the activity of other endogenous

growth factors, Kirkpatrick seeks to identify compounds that inhibit the activity of thioredoxin (column 3, lines 4-7 and column 8, lines 2-19).

The redox state of thioredoxin is modulated by the interplay between itself and an NADPH-dependent selenium containing enzyme, thioredoxin reductase, that catalyses the reduction of thioredoxin. As shown schematically by Figure 5, thioredoxin reductase has two active site cysteines, Cys-135 and Cys-138 and thioredoxin has three reactive cysteines, Cys-32 and Cys-35 located at the active site and Cys-73 located outside of the active site.

Kirkpatrick performed extensive testing of the asymmetrical disulfide compounds to understand how these compounds affect the thioredoxin reductase/thioredoxin redox system. In particular, the effects of five 2-imidazolyl disulfides listed on Table 1 are the most fully characterized. To fully appreciate the complexity of this system, one needs to appreciate that an asymmetric compound of the general formula R1-SS-R2 is capable of and in fact does react with each and every cysteine of both thioredoxin and thioredoxin reductase (Kirkpatrick, column 11, lines 47-55). However, as Kirkpatrick teaches, only disulfide compounds that irreversibly react with Cys-73 of thioredoxin possess in vivo anti-tumor activity (column 11, lines 53-59). The reactions with the other four cysteines in the active sites of both thioredoxin and thioredoxin reductase are reversible and do not appear to translate to an in vivo effect. Thus, the challenge described by Kirkpatrick is how to discern which disulfide compound is capable of irreversibly modifying Cys-73 of thioredoxin.

Focusing on just thioredoxin, electrophoretic and mass spectral analysis show that one to three cysteines are modified in a concentration dependent manner (column 11, lines 40-45). As schematically illustrated by Figure 5B, the initial reaction appears to be fast and directed to one of the active site cysteines (Cys-32) which is followed by the formation of a disulfide bridge between Cys-32 and Cys-35. A second reaction occurs more slowly at Cys-73 which is located outside of the active site and it is this reaction that appears to be responsible for the in-vivo anti-tumor activity. In order to interpret the data, a time course is performed (to tease apart the fast initial reversible reaction from the slow irreversible reaction) and this time course must be performed on wild type

thioredoxin, a thioredoxin mutant where the active site cysteines are mutated to serine, and a thioredoxin mutant where Cys-73 is mutated to serine.

As a result of the complexities of identifying compounds that affect the thioredoxin/thioredoxin reductase enzymes, one of skill in the art would not have been motivated to assay a mixture of asymmetrical disulfide compounds against this system. For starters, a mixture of asymmetric disulfide compounds would undergo disulfide exchange. That is, if a mixture of two compounds of Kirkpatrick were tested, the compounds themselves would form a mixture of different compounds so one would not know what compound or compound was responsible for the signal. Moreover, the different compounds would be present in the mixture in varying amounts depending on the individual group's reactivity making it impossible to compare pools of compounds with each other to see which pool may be worth following up further. For example, one pool with a relatively large amount of a relatively weak inhibitor would give the same strength of signal as another pool with a relatively small amount of a relatively strong inhibitor. As a result, with the uncertainty surrounding the multiple assays that would be required to make sense of the thioredoxin/thioredoxin reductase enzymes and the potential for disulfide exchange between the test compounds, one of skill in the art would not have been motivated to test the asymmetrical disulfide compounds of Kirkpatrick in mixtures as taught by Konings.

Konings does not remedy the deficiencies of Kirkpatrick

In contrast, the Konings article uses RNA hybridization as model to study combinatorial chemistry. Due to the complementary nature of nucleic acid base pairing, one of ordinary skill in art would expect the test RNA's to interact with the target RNA but not with another test RNA. This contrasts with the compounds of Kirkpatrick, which due to their thiol/disulfide exchange mechanism, would be reactive with one another. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in combining Kirkpatrick with Konings.

The Office Action alleges that Konings at page 2710, column 1, paragraph 2, states "that the method is generally applicable to all compounds . . . which would include the disulfide structures disclosed by Kirkpatrick." Applicants respectfully urge that there

is no such statement "that the method is generally applicable to **all** compounds" (Emphasis added.) Instead, Konings states that "[f]ixed position pooling bas been used for libraries synthesized using a variety of chemistries (Figure 1), and iterative deconvolution strategies have been used to identify a single active compound from a mixture." This statement is not equivalent to "that method is generally applicable to all compounds." Indeed, none of the representative compounds of Konings given in Figure 1 or citations 8-20 are disulfides or compounds that would be reactive with one another. Figure 1 discloses *N*-methyl peptides, phosphoryl-linked compounds and (mercaptoacyl)proline derivatives. References 8-20 relate to the following types of compounds: oligonucleotides (Reference No. 8), guanosine quartets (Reference Nos. 9, 18 and 19), peptides or synthetic peptides (Reference Nos. 10-17) and phosphodiesters (Reference No. 20). See Konings, pages 2718-2719. Thus, Konings does not give one of ordinary skill in the art motivation to arrive at the present invention.

Kirkpatrick and Konings do not teach or suggest all of the elements of the claims and most certainly do not establish a reasonable expectation of success

As stated above, due to the difficulty in assaying a compound's effect on the thioredoxin/thioredoxin reductase redox system and the disulfide exchange that would occur among any members of asymmetrical disulfide agents that are combined together, a mixture of disulfide active agents would not produce meaningful data. Therefore one of skill in the art would have had a reasonable expectation of success in the combination of employing mixing together the disulfides of Kirkpatrick.

Claims 34, 53, 54 and 58 are rejected under 35 USC 103(a) as being obvious over US Patent No. 6,552,060 (Kirkpatrick) and Konings, *J. Med. Chem.* 1996, 39, 2710-2719 and US Patent No. 4,766,133 (Fischli). Applicants urge that the claims are patentable over this combination of references for the following reasons. As stated above, the combination of Kirkpatrick and Konings does not (1) teach or suggest all of the elements of the claims, (2) provide a reasonable expectation of success or (3) motivate one of ordinary skill in the art to combine the references. Fischli does not remedy any of these deficiencies.

Kirkpatrick, Konings and Fischli would not have motivated one to arrive at the present invention

The Office Action alleges that "one of ordinary skill in the art would have been motivated to use the compounds disclosed by Fischli et al. because Fischli et al. teach that their disulfides are 'gastric secretion-inhibiting and/or muscosa protecting' [cite omitted], which would be beneficial because Kirkpatrick et al. and Konings et al. teach the therapeutic application of disulfides to the stomach and/or gastrointestinal tract would require such protection."

In responding to this allegation, applicants first wish to clarify that Konings is a paper discussing theoretical combinatorial chemistry using RNA hybridization as a model and does not discuss either disulfides or stomach cancer. Also, Kirkpatrick does not suggest that administration of an anti-cancer drug to the stomach "would require" or even benefit by a combination therapy with a gastric secretion-inhibiting and/or muscosa protecting drug. In fact, Kirkpatrick defines combination therapy as follows in column 4, lines 47-56:

> Combination therapy (i.e., chemotherapy) using two or more therapeutic drugs to treat malignant tumors in humans is specifically contemplated herein. For cancer, therapeutic or anti-cancer drugs may include anti-metabolites, alkylating agents, antibiotics, tubulant binders, etc. Combinations of drugs are administered in an attempt to obtain a synergistic cytotoxic effect on most cancers, e.g., carcinomas, melanomas, lymphomas and sarcomas, and to reduce or eliminate emergence of drug-resistant cells and to reduce side effects to each drug.

Kirkpatrick is completely silent on gastric secretion-inhibition and muscosa protection when treating stomach cancer.

Moreover, the teachings of Kirkpatrick (that some types of disulfides have anti-cancer properties) and of Fischli (that some disulfides inhibit gastric secretion), would not have provided motivation for one of ordinary skill in the art to combine Kirkpatrick and Fischli. Konings, which discusses theoretical combinatorial chemistry using RNA hybridization as a model, does not remedy the deficient combination of Kirkpatrick and Fischli. Applicants also note that Fischli is completely unrelated to combinatorial chemistry and therefore cannot remedy the deficient combination of Kirkpatrick and Konings.

Kirkpatrick, Konings and Fischli would not have established a reasonable expectation of success

The Office Action states that "one of ordinary skill in the art would have reasonably expected to be successful because all three references teach the application of similar compounds (e.g., all three references teach asymmetric disulfides)."

In response to this allegation, applicants wish to first of all clarify that the Konings reference discusses theoretical combinatorial chemistry using RNA hybridization as a model and does not discuss asymmetrical disulfides. Also, as discussed above, one would not have had motivation or a reasonable expectation of success in testing the compounds of Kirkpatrick as mixtures as suggested by Konings. Fischli, which is silent on combinatorial chemistry, does not remedy this deficiency to provide the requisite motivation or a reasonable expectation of success.

Kirkpatrick, Konings and Fischli do not teach or suggest all of the elements of the claims

Fischli does not discuss disulfide compounds that have CTBF's and therefore does not teach all of the elements of the claims or provide motivation to arrive at the present invention.

Conclusion

Applicants urge that the present claims are in condition for allowance. The Examiner is invited to contact the undersigned by telephone to advance prosecution of this application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

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Date

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